

Physicians Guide



to the Management of Huntington's Disease



**Huntington's
Disease**
Association of Ireland

A PHYSICIANS GUIDE TO THE MANAGEMENT OF HUNTINGTON'S DISEASE

2nd Edition

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Preface

Huntington's disease remains a daunting problem for patients and families, and for physicians. A doctor caring for patients in a community setting may have seen only one or two previous cases. The information found in this guide may help foster a sense of hope.

Huntington's disease is a well-studied condition and, although there have been few systematic trials of the interventions we will suggest, this book is the product of many years of both research and hands-on experience. We have organised this edition, like its predecessor, around the three general manifestations of Huntington's disease: motor abnormalities; cognitive changes; and various psychiatric disturbances. We provide several generally accepted pharmacological and non-pharmacological treatments for each problem. In addition, the national lay organisations, such as the Huntington's Disease Society of America (HDSA) and the Huntington Society of Canada (HSC), and their local branches, are also excellent sources of information and assistance for patients, family members, caregivers, physicians, and other health care professionals.

Major changes from the first edition include the addition of a section on the genetics of HD and the use of both confirmatory and presymptomatic testing; a reworking of the section on psychiatric disorders to reflect major changes in the available medications over the last several years; and, the expansion of the cognitive section to include more recommendations about coping skills and management of behavioural problems.

There are many incurable diseases, such as diabetes mellitus, emphysema or HD. It is important to remember that incurable does not mean untreatable, that even untreatable diseases may have treatable consequences, and that patients and their families can still benefit greatly from an accurate diagnosis, prognosis, education and support. It is our hope that, with the aid of this guide, a physician meeting someone with Huntington's disease will not say "You've got HD....there's nothing you can do about it," but instead will be able to say, "You've got HD and I can help".

Preface UK

Huntington's disease is a serious condition but, as yet, there is no treatment to delay its onset or to slow the neurodegenerative process. Despite this, there is still much which can be done for patients and their families. One issue is that HD is relatively uncommon so most professionals will see only a few patients over the course of their working lives. "The Physicians Guide" has proved a valuable resource in giving practical suggestions in the management of difficult problems. I am confident that the second updates edition will be equally popular.

A remarkable aspect of working on HD is the way in which leading scientists, clinicians and lay-organisations co-operate. This booklet is evident of that spirit. The Huntington's Disease Society of America generously allowed its sister organisation to republish the booklet.

Huntington's Disease Association UK would like to thank the many people who carefully read and re-read the text so that drug names and practices were described in a way appropriate for those of us who work in the British health and social services system. HDA is particularly grateful to Dr. Neil Glendinning, Dr. Ken Barrett, Dr. Hugh Richards, Ms Sue Watkin and Mrs Cath Stanley for their help with this work.

Finally, the Huntington's Disease Association hopes the booklet will continue to prove its worth as a resource for those who care for HD patients and their families in whatever setting: General Practice, hospital out-patients, care at home or in nursing homes.

Oliver Quarrell, Sheffield, June 2002
Updated April 2009

Huntington's Disease Association is grateful to all of those who contributed towards updating this useful publication in 2009. Particular thanks go to Dr Sarah Tabrizi, Dr Roger Barker, Professor Anne Rosser, Dr Oliver Quarrell and Sue Smith for reviewing and updating this edition.

Cath Stanley

Disclaimer - The indications and dosages of this material have either been recommended in the medical literature or conform to the practices of physicians expert in the care of people with Huntington's disease. The indications do not necessarily have specific approval from the Food and Drug Administration (FDA) for the indications and dosages for which they are recommended. The package insert for each drug should be consulted for uses and dosage approved by the FDA. Because standards for dosage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Statements and opinions expressed in this book are not necessarily those of the Huntington's disease Society of America, Inc. nor does HDSA promote, endorse, or recommend any treatment or therapy mentioned herein. The lay reader should consult a physician or other appropriate health care professional concerning any advice, treatment or therapy set forth in this book.

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1. OVERVIEW AND PRINCIPLES OF TREATMENT

OVERVIEW

Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by an expansion in the IT-15, or huntingtin, gene on chromosome 4, which encodes the protein huntingtin. HD is inherited in autosomal dominant fashion, so that each child of an affected parent has a 50% chance of developing the disease. Most people with HD develop the symptoms in their forties and fifties, although there may be subtle changes much earlier. About 10% of patients have onset of symptoms before age 20 (juvenile HD) and 10% have onset after age 60.

Huntington's disease manifests as a triad of motor, cognitive, and psychiatric symptoms which begin insidiously and progress over many years, until the death of the individual. The average survival time after diagnosis is about fifteen to twenty years, but some patients have lived thirty or forty years with the disease.

The **movement disorder** is characterised both by the emergence of involuntary movements, or chorea, and by impairment of voluntary movements. This latter impairment often contributes more to disability than the chorea itself, resulting in reduced manual dexterity, slurred speech, swallowing difficulties, problems with balance, and falls. Both chorea and impairment of voluntary movements progress in the middle stages of HD, but later, chorea often declines as patients become rigid and unable to initiate voluntary movements. Patients in this advanced state are unable to care for themselves.

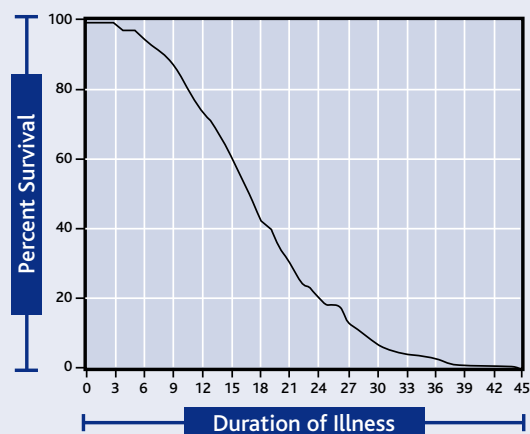
The **cognitive disorder** is characterised initially by a loss of speed and flexibility. This may be seen first in complex tasks, when the patient is unable to keep up with the pace and lacks the flexibility required to alternate between tasks. Cognitive losses accumulate and patients develop more global impairments in the later stages of the disease.

The most common specific **psychiatric disorder** in HD is depression. Patients may also suffer from mania or obsessive compulsive disorder. Other symptoms (which may not fit a specific psychiatric category) include irritability, anxiety, agitation, impulsivity, apathy, social withdrawal and obsessiveness.

HD can be roughly divided into three stages. Early in the disease, patients are largely functional and may continue to work, drive, and live independently. Symptoms may include minor involuntary movements, subtle loss of coordination, difficulty thinking through complex problems, and perhaps a depressed or irritable mood. In the middle stage, patients will probably not be able to work or drive and may no longer be able to manage their own finances or perform their own household chores, but will be able to eat, dress, and attend to personal hygiene with assistance. Chorea may be prominent, and patients will have increasing difficulty with voluntary motor tasks. There may be problems with swallowing, balance, falls, and weight loss. Problem solving becomes more difficult because patients cannot sequence, organise, or prioritise information.

In the advanced stage of HD, patients will require assistance in all activities of daily living. Although they are often nonverbal and bedridden in the end stages, it is important to note that patients seem to retain fair comprehension. Chorea may be severe, but more often it has been replaced by rigidity, dystonia, and bradykinesia. Psychiatric symptoms may occur at any point in the course of the disease, but are harder to recognise and treat late in the disease.

Survival of HD patients over time



HD with onset in childhood has somewhat different features. Chorea is a much less prominent feature, and may be absent altogether. Initial symptoms usually include attentional deficits, behavioural disorders, school failure, dystonia, bradykinesia, and sometimes tremor. Seizures, rarely found in adults, may occur in this juvenile form.

Juvenile-onset HD tends to follow a more rapid course, with survival less than 15 years. The vast majority of patients with juvenile onset have inherited their HD gene from an affected father. The reason for this tendency is now understood in genetic terms and will be explained in detail in chapter 2.

The HD gene was identified in 1993. It contains a repeating sequence of three base-pairs, called a triplet repeat. An excess number of CAG repeats in the gene results in a protein containing an excess number of glutamine units. The normal function of huntingtin is not known, but the expansion of the huntingtin gene is likely to be a so-called "gain of function" mutation. In HD, huntingtin protein encoded by the abnormal gene collects in the nucleus of the cell, giving rise to a structure called an inclusion body. Similar intranuclear inclusions have been seen in other neurodegenerative disorders caused by polyglutamine expansions. The mechanism by which the protein aggregation may cause a brain disorder is not fully understood. The neurons may first become dysfunctional then undergo progressive degeneration and die. Certain neurons appear to be more vulnerable in HD. Atrophy is most marked in the corpus striatum of the basal ganglia, including the caudate and putamen. In later phases of the disease, other regions of the brain may be affected.

The clinical diagnosis of HD is made on the basis of the family history and the presence of an otherwise unexplained characteristic movement disorder, and is usually confirmed by a gene test. The gene test can be particularly useful when there is an unknown, or negative family history (as occurs in cases of early parental death, adoption, misdiagnosis, or non-paternity) or when the family history is positive, but the symptoms are atypical. The discovery of the huntingtin gene has greatly simplified the diagnostic evaluation of an individual suspected to have HD. The implications of the diagnosis of HD for the patient and family are profound, and provision should be made for genetic counselling of individuals affected by the results. Genetic counselling and genetic testing are discussed more fully in chapter 2. It is important to remember that the gene test only determines whether or not the HD-causing genetic expansion is present, and not whether an individual's current symptoms are caused by the HD gene.

HD remains a clinical diagnosis. The motor disorder can be delineated and followed longitudinally using a quantitative examination designed for HD, such as the

Quantified Neurological Examination, or the Unified Huntington's Disease Rating Scale, which also includes a useful scale for functional capacity. The Mini-Mental State Examination is useful in following the cognitive disorder longitudinally, but it lacks sensitivity in certain areas which are affected in Huntington's disease and may be supplemented by a more sophisticated cognitive battery such as the Mattis Dementia Rating Scale.

PRINCIPLES OF TREATMENT

Caring for patients with HD is both challenging and rewarding. At times, the lack of definitive treatments can be frustrating, but careful attention to the changing symptoms and good communication between professionals, family members, and affected individuals all contribute to the successful management of the disease.

HD is a progressive disease. The symptoms evolve over time such that treatments which were effective in the early stages may be unnecessary, or problematic later on, and vice versa. For example, medications such as neuroleptics may be started in the early to middle stages to control chorea. However, this category of medications may exacerbate the rigidity and bradykinesia of the later stages, and result in delirium or oversedation as the cognitive disorder progresses. The medication list and the rationale for each medication needs to be reevaluated at regular intervals. Sometimes the most helpful intervention a physician can perform is to discontinue an unnecessary drug.

Symptoms vary over time as a patient passes through different stages of the disease. Symptoms also vary from individual to individual, even within a family. For example, one patient may develop a severe mood disorder, requiring multiple hospitalisations, but have little motor disability. The patient's brother may have debilitating motor symptoms, but no mood disturbance at all. Thus interventions need to be tailored to individual symptoms, and fearful patients should be reassured that their symptoms may not necessarily resemble those of their relatives.

HD patients, like others with injuries to the brain, are highly vulnerable to side effects, particularly cognitive side effects, of medications. The physician should begin with low doses and advance medicines slowly. Polypharmacy should be avoided where possible.

Many of the drugs used in treating symptoms of HD, such as neuroleptics and antidepressants, will not have immediate efficacy and patients need to be told that they may feel worse before they feel better, because they will experience the side effects, before the beneficial effects have appeared.

Pharmacologic interventions should not be launched in isolation, but in a setting of education, social support, and environmental management. Symptomatic treatment of HD needs to be approached like any other medical problem. The clinician should elicit the details of the symptom, its character, onset and duration, and its context including precipitating, exacerbating and ameliorating factors. A differential diagnosis should be generated, non-pharmacologic interventions should be considered, and the clinician should have a way of determining whether the goals of treatment are being met and should formulate a contingency plan if treatment is not working. Sharing some of this reasoning process with patients and families can be reassuring.

Patients with HD will often be accompanied by a caregiver on visits to the doctor. This caregiver can be a crucial informant, particularly in the later stages of the disease, when speech and cognitive difficulties may prevent patients from supplying a history. However, both patient and caregiver may not feel comfortable discussing certain important issues in each other's presence, such as irritability, driving, relationship, or sexual problems. Therefore an effort should be made to speak to both individuals alone during the visit.

A few words should be said on the issue of "alternative treatments" for Huntington's disease - unproven remedies such as herbs, megadose vitamins, homeopathic preparations, or magnetic devices, which are to be distinguished from experimental treatments taking place as part of a scientific study. Patients should be encouraged to discuss their ideas about these therapies and not to be afraid to tell their physicians that they are trying them. This will allow the doctor to help the patient think through the pros and cons of such a decision, to avoid notoriously dangerous or ineffective nostrums, and to monitor for side effects. Patients should understand that there is no substance, no matter how "natural," which has pharmacologic activity without side effects, and that all treatments carry an element of risk.

We have found it useful to share certain caveats with patients to minimise the risk for those who have chosen to pursue these alternative therapies:

1). Don't spend too much money 2). Don't do something that common sense suggests is dangerous and 3). Don't neglect or discontinue effective medical treatments in favour of an unproven therapy. By following these principles patients are likely to avoid harm.

Physician's looking for information on specific treatment trials for their patients may wish to contact the National Voluntary organisation (Appendix 3).

2. GENETICS

GENETIC COUNSELLING

The discovery of the gene has led to new insights about HD. Not all patients or family members will want or need genetic testing, but all should be offered genetic counselling. A referral can be made by the physician to the genetic counsellor. Here are some of the issues that may be explained:

Basic genetics - inheritance pattern

HD is an autosomal dominant disease, which means it affects males and females with equal likelihood. Each child of an affected individual has the same 50% chance of inheriting the abnormal huntingtin gene, and therefore developing the disease at some stage.

The Huntingtin (IT-15) gene and the Huntingtin protein

The Huntingtin gene directs the cell to make the huntingtin protein, whose function is unknown. Huntingtin protein contains a sequence in which the amino acid glutamine is repeated a number of times. These glutamine residues are encoded in the gene by the DNA trinucleotide "CAG." The number of times that "CAG" is repeated (the CAG repeat number) determines the number of consecutive glutamines in that segment of the huntingtin protein. The huntingtin protein is made in normal amounts, whether it has a normal or excess number of glutamines, but it appears to be processed differently when it has an excess number of glutamines, so that the protein accumulates in the neuron. The details of this process and how it relates to the development of neurologic disease are currently being studied.

CAG repeats in the Huntingtin gene

The normal and abnormal CAG repeat number ranges have been determined only by clinical experience, which includes that of about 10,000 affected and unaffected individuals worldwide. Normal huntingtin genes contain 10-35 "CAG repeats." Repeat sizes of 27-35 are at the upper end of the normal range, and will not result in Huntington's disease, but sometimes increase into the abnormal range in future generations, particularly if passed on by a male. The risk for this event has not been quantified. 36-39 repeats are at the low end of the abnormal range; an individual with this result may develop Huntington's disease or may live a normal lifespan without developing the condition. People with 40 or more repeats will develop Huntington's disease if they live a normal life-span.

CAG repeat number and age of onset

There is a rough inverse correlation between the CAG repeat number and the age of onset of HD symptoms. However, the CAG repeat number accounts for only about half of the variation in age of onset. The age of onset cannot be accurately predicted from CAG number alone. The CAG number also does not accurately predict what symptoms an individual will have, or how severe or rapid the course of the disease will be.

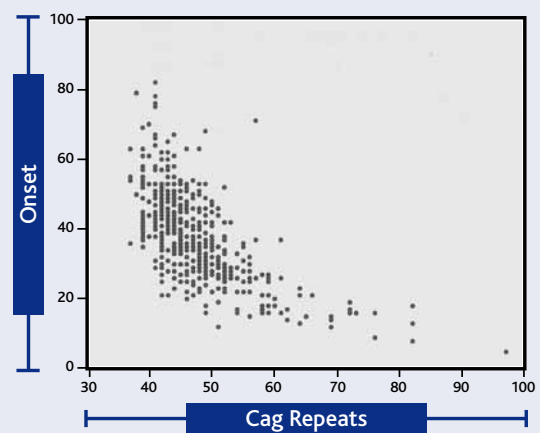
Instability of the CAG repeat number

Genes with expanded CAG repeat sizes are prone to expand further as they are passed on to a child, particularly in the case of paternal transmission, although expansions can occur in maternal transmission as well. Thus, children who inherit the abnormal gene often have a larger repeat number than the affected parent, and may consequently tend to develop symptoms at a younger age. The earlier onset of symptoms in a child than a parent is called anticipation. In rare cases, symptoms may be evident in the child while the parent is still asymptomatic.

Absent family history of HD

Some individuals develop HD without ever knowing they were at risk, because they have no known family members with the disease. This occurs in 2-5% of all cases. Sometimes this can be explained by early death of a parent who carried the gene, but did not live long enough to manifest the symptoms, by adoption, or by mistaken paternity.

Correlation of age of onset with triplet repeat length



Others represent "new mutations," caused by rare expansions of parental genes with a high-normal CAG repeat number (27-35 repeats) into the affected range in the child. Individuals with high normal CAG repeat sizes are not themselves at risk for developing HD. Our understanding of the significance for their offspring is likely to improve, and they may be best referred to someone with specialised knowledge, such as a genetic counsellor.

GENETIC TESTING

With the discovery of the gene, an accurate genetic test became available. The Huntington's disease gene test usually requires a blood sample, but can be performed on other tissues, such as skin, amniocytes or chorionic villus cells, or autopsy material. The test requires special molecular diagnostic facilities, which are available via the National Centre for Medical Genetics, www.genetics.ie as listed in appendix 2.

Genetic testing for HD is potentially useful in three clinical situations: diagnostic, or confirmatory testing; predictive, or presymptomatic testing; and prenatal testing.

Diagnostic testing

Diagnostic genetic testing refers to the use of a gene test in a patient who has symptoms suggestive of HD, with or without a family history. If the clinical suspicion is strong, this may be the only diagnostic test needed.

It is important to remember that the presence of the Huntingtin gene with an increased repeat number may not mean that a patient's current symptoms are caused by HD. The diagnostic test should be used sparingly, and only when the neurologic symptoms strongly suggest the onset and progression of HD.

Confirmatory testing should be performed in a patient who appears to have HD if no other affected family members have previously had a gene test, to be sure that the "family disease" is really HD and not some other condition. Diagnostic genetic testing is also very useful in the evaluation of an individual who appears to have HD but who has a negative or absent family history.

A special note should be made about the effects of an individual's gene test on the individual's family. The presence of an expanded HD gene in one individual has direct implications for that person's children, siblings, and perhaps his parents and collateral relatives. Consent always has to be sought by the physician from the individual or next of kin before the sample can be processed. Any physician who diagnoses HD in a patient must be prepared to face questions from and about these additional family members. Consultation with a genetic counsellor may help to make this difficult situation easier.

Predictive testing

Predictive testing refers to the use of an HD gene test in a person who has no symptoms but wants to know whether or not they carry the expanded gene. Predictive testing of healthy individuals requires a different clinical approach than the one to which physicians and patients are most accustomed. There are no direct medical indications for or benefits from a predictive test. There are also potential psychosocial risks to predictive testing, including adverse effects on the individual's mood, on relationships with friends and family and on insurability and employability.

Predictive testing should be reserved for competent adults who have participated in a careful discussion of their genetic risks and the potential risks and benefits of the test itself.

The World Federation of Neurology, the International Huntington Association, and the Huntington's Disease Society of America have published guidelines regarding the genetic and psychological counselling and support that should surround predictive testing. In keeping with these guidelines, Huntington's disease predictive testing is available at the National Centre for Medical Genetics, www.genetics.ie as listed in appendix 2.

Referral of interested family members to a predictive test centre is highly recommended.

Prenatal testing

Prenatal testing for HD is possible in some countries, and should be performed in conjunction with detailed genetic counselling. Affected or at-risk individuals or couples should be informed of all of their reproductive options (shown in table 1), with the understanding that different options are appropriate or desirable for different people.

For those who desire prenatal testing, the best time to make arrangements is prior to the pregnancy. Chorionic villus sampling can be performed from about 11 weeks of pregnancy. A non-disclosing prenatal test, which determines only whether the fetus received a chromosome from the affected grandparent or the unaffected grandparent, without determining whether the foetus or at-risk parent actually carries the HD gene, requires samples from several individuals, therefore, the preparation time is longer but the pre-natal test can be done from 11 weeks.

Preimplantation Genetic Diagnosis (PGD) offers another alternative to testing for HD in pregnancy (prenatal testing). PGD gives a couple the chance of conceiving a pregnancy that should be unaffected by HD. PGD involves the couple undergoing IVF treatment even if they are a normally fertile couple. The main aim of the treatment is to create embryos using the eggs and sperm of the couple involved. These embryos are then tested for HD before they are implanted in the women's womb. Only embryos without the HD mutation are suitable for replacement. The hope is then that the couple will be successfully pregnant with a baby that is not at risk of inheriting the HD gene. PGD can also be offered in a non-disclosing way, if the parent at 50% risk does not want to have a predictive test.

Although PGD does offer an acceptable way forward for many couples, it is not an easy option. The success of taking home a baby is relatively low (around 1 chance in 5 at the outset and 1 chance in 3 if the stage of embryo transfer is reached). Also the testing of the embryos is not 100% accurate and if couples do become pregnant there is a small error rate. The work up for PGD is complex, time consuming and expensive. Couples should be referred to their local genetics service for further information.

HDAI would like to thank Rosemarie Kelly, Genetic Counsellor, National Centre for Medical Genetics for her review of, and updates to, this Genetics chapter.

Table 1: Reproductive options

- Natural reproduction without genetic testing
- Prenatal testing by amniocentesis or chorionic villus sampling
- Non-disclosing prenatal test
- Decision not to reproduce (may include sterilisation)
- Artificial insemination
- Adoption
- Surrogate mother
- Pre-implantation genetic testing and embryo selection

3. THE MOVEMENT DISORDER

INTRODUCTION

There are two parts to the movement disorder associated with Huntington's disease: the presence of involuntary movements, and the impairment of voluntary movements. The involuntary movements are called chorea, or choreoathetosis, and consist of irregular jerking or writhing movements. Chorea is the most noticeable feature of HD. In fact, the condition is often referred to as Huntington's chorea, yet the impairment of voluntary movement is more highly correlated with functional disability. Abnormal eye movements (interrupted pursuit and slow, hypometric saccades), slow and uncoordinated fine movements, dysarthria, gait disturbance, and dysphagia can be largely independent of chorea and may limit a person's ability to work, care for himself, and communicate. Although it is tempting to treat the highly noticeable chorea of Huntington's disease right away, it is important to remember that the drugs used to suppress chorea can have disadvantages of their own, including worsening of voluntary motor disturbance.

Table 2: Principles of treatment of the movement disorder

- Consider non-drug interventions first.
- Pharmacologic treatment of chorea may worsen other aspects of the movement disorder, cognition, or mood.
- Chorea may diminish over time, reducing the need for treatment.

CHOREA

Many patients are not bothered by their chorea and may not even be aware of most of the movements. The physician and patient first need to establish whether the chorea requires any treatment at all. Is the chorea severe enough to interfere with voluntary activities such as writing, cooking, or eating? Does severe chorea seem to be causing falls or accidents? Is highly visible chorea a significant source of distress for the patient?

Before beginning medication for chorea, non-pharmacological interventions should be considered. Chorea, like most forms of involuntary movement, is worsened by stress, anxiety, or depression, is decreased during sleep, and often varies with posture or positioning. Treatment of underlying mood and anxiety disorders, and providing a calm, predictable environment are a first step. Various assistive devices may be helpful. These include padded, reclining chairs, padding for the bed, and wrist and ankle weights to reduce the amplitude of the chorea. Occupational Therapists or HDAs can provide information.

Doctor and patient also need to have realistic expectations for pharmacotherapy. Medications will not alter the progression of the underlying illness. They will not improve speech or the ability to swallow, prevent falls, or improve fine motor control. In fact, drug-related side effects such as sedation and rigidity may increase the risk of falls and decrease the intelligibility of speech. However, reduction of severe chorea may improve gross motor control and may be of cosmetic value.

Akathisia is an extremely uncomfortable internal sense of restlessness, sometimes induced by neuroleptics, which may cause patients to pace, or be unable to sit still. It can be mistaken for agitation or anxiety, prompting the physician to increase the dose of the offending drug, creating a vicious cycle. In the same way, a parkinsonian tremor and occasionally myoclonus may be seen, of which the former will be made worse by anti-choreic drugs such as atypical neuroleptics.

The movement disorder of HD changes over time. In most patients chorea eventually peaks and then begins to decline, while rigidity and bradykinesia become more significant. At this point, the drugs that helped to suppress chorea may no longer be needed, and in fact may worsen HD-related rigidity. Therefore it is important to assess the need for anti-chorea medication at regular intervals, and perhaps to make periodic trials of dose reduction or discontinuation.

Table 3: Medications used to suppress chorea

Class	Medication	Starting dose	Maximum dose	Adverse effects
Neuroleptics	Olanzapine	2.5mg at night	15-20mg per day	Sedation, parkinsonism, akathisia, raised triglycerides, weight gain from increased appetite. Caution should be exercised in patients with Diabetes and blood glucose monitored.
	Risperidone	0.5-1mg/day	6mg/day	As above but less effect on increasing appetite.
	Quetiapine	25mg od	750mg/day	As above but less effects on lipids and glucose.
	Sulpiride	50-100 mgs/day	2400mg/day	Agitation, dystonia, akathisia, sedation, hypotension, dry mouth, constipation.
	Haloperidal	0.5-1mg/day	6-8mgs/day	Sedation, more parkinsonism, dystonia, akathisia, hypotension, constipation, dry mouth, weight gain.
Benzodiazepines	Clonazepam	0.5mgs/day	4mgs/day	Sedation, ataxia, apathy, cognitive impairment may be exacerbated, withdrawal seizures.
	Diazepam	1.25mgs/day	20mgs/day	Same as above.
Dopamine depleting agents	Tetrabenazine	12.5mgs once a day and titrating slowly up	200mgs/day	Depression and sedation.

Three classes of medication are commonly used to suppress chorea in Huntington's Disease: **neuroleptics**, such as Olanzapine and Risperidone; **benzodiazepines**, such as Clonazepam and Diazepam; and **dopamine depleting agents**, such as Tetrabenazine. Each class has its advantages and disadvantages. Of note, there is currently little systematic trial data on the relative efficacy of the various treatment options for chorea, and that the recommendations in this booklet are based on expert opinion.

The suppression of movement regarded as a side effect when neuroleptics are used to treat psychosis, is the desired effect when they are used to treat chorea.

Previously the more old fashioned neuroleptics such as Haloperidol were frequently used, but now, in clinical practice, the most common neuroleptics to use for treatment of chorea are the atypical anti-psychotics, namely Olanzapine, Risperidone and Quetiapine. Olanzapine and Risperidone are most commonly prescribed. These have the advantage in that they are probably better tolerated than the older anti-psychotics and cause less unwanted extra-pyramidal symptoms, such as unacceptable rigidity and dystonia. They also encourage weight gain which can be an advantage in this condition as well as helping patients sleep and calming down their mood swings. Tardive dyskinesias are less with these drugs.

They should be started at the lowest dose, and gradually titrated up as needed. Glucose and lipids should be checked in subjects on Olanzapine and Risperidone as these drugs are associated with an increased risk of stroke in elderly patients with dementia. It is important to consider a history of stroke or transient ischemic attack in the older Huntington's Disease patient, before using Olanzapine and Risperidone. Sulpiride is useful, but can cause side effects of agitation and Parkinsonism. Haloperidol may still be used, but has the most significant parkinsonian side effects and the risk of tardive dyskinesias is higher. Tardive dyskinesia is a syndrome of voluntary movements, often first noticed in the face and mouth that develops in some patients taking neuroleptics. Tardive dyskinesias are of concern because the symptoms are usually permanent, and will likely be hard to recognise in someone with HD.

All neuroleptics have a risk of neuroleptic malignant syndrome, but this is less with the newer atypical anti-psychotics such as Olanzapine, Quetiapine and Risperidone. Neuroleptic malignant syndrome is a rare, but life threatening reaction characterised by acute onset of delirium, rigidity, and fever, often accompanied by leukocytosis and elevated CPK. Families should know about this so that the patient can be given prompt medication attention if this develops. This is more associated with the older neuroleptics, such as Haloperidol.

Dopamine depleting agents, such as Tetrabenazine, are also a treatment for chorea. Tetrabenazine shows some of the side effects of neuroleptics, but tend to be milder, and has not been shown to cause tardive dyskinesias. Tetrabenazine is effective at treating chorea, it is best started at 12.5mg twice a day or three times a day, and increased as needed. A recognised side effect of Tetrabenazine is depression, which is a common feature of Huntington's Disease and does need to be kept an eye on.

Benzodiazepines can be used for treatment of chorea, but their sedating actions and effect on cognition can be a disadvantage.

Other agents have been tried for the chorea in HD including amantadine. This drug can be given at an initial dose of 100mg od increasing up to 400mg a day. the main side-effects are ankle oedema, and worsening confusion along with livedo reticularis in some cases.

RIGIDITY, SPASTICITY AND DYSTONIA

Rigidity and spasticity tend to emerge later in the course of Huntington's disease, except in cases of childhood onset, in which they are often present from the beginning. They can impair gait, lead to falls, and necessitate the use of a wheelchair. Dystonia may include twisting, tilting or turning of the neck (torticollis), involuntary arching of the back (opisthotonos) and arching of the feet. It may be a symptom of HD, or a side effect of neuroleptic therapy.

A variety of medications have been used to treat rigidity, spasticity, and dystonia, all with modest success at best. Benzodiazepines, such as clonazepam, or baclofen, starting at 10mg/day and increasing up to 90mg may relieve stiffness, but may also increase bradykinesia. Tizanidine, a clonidine like drug, is sometimes helpful for spasticity, beginning with 2mg qds and increasing every 4-7 days to a maximum of 12-24mg in divided doses but you can go up to 36mg if need be.

Antiparkinsonian medicines such as amantadine 50-200mg/day or levodopa/carbidopa 25/100mg two to three times per day. All of these medicines may cause delirium and may lose their efficacy after several months if they have any benefit at all. Consultation with a physiotherapist to design a programme to mobilise the patient and prevent contractures may be an important component to the management of rigidity and spasticity. Botulinum toxin injections have been used rarely, but might be beneficial if severe rigidity of a small muscle or group of muscles is disturbing function.

MYOCLONUS, TICS AND EPILEPSY

Myoclonus, sudden brief jerks involving groups of muscles, is more common in juvenile-onset HD, where it may be mistaken for a seizure. Like chorea, myoclonus may not be disabling or particularly distressing, but may respond to treatment with Clonazepam, Sodium Valporate or Levetiracetam if treatment is necessary. Tics are brief, intermittent stereotyped movements such as blinking, nose twitching, head jerking, or transient abnormal postures. Tics which involve the respiratory and vocal apparatus may result in sounds including sniffs, snorts, grunts, coughs, and sucking sounds.

Patients may be unaware of vocal tics, but family members may find the incessant noises grating. They should be helped to understand that the tics are not under voluntary control. Tics generally do not by themselves require treatment, but may respond to neuroleptics, benzodiazepines, or SSRIs.

Epilepsy is uncommon, though not unheard of, in adults with HD, but is said to be present in 30% of individuals with juvenile-onset HD. A first seizure in an HD patient should not be attributed to HD without further evaluation as it may be indicative of an additional neurologic problem, such as a subdural hematoma sustained in a fall. The workup of a first seizure should include a complete exam, laboratory studies to rule out an infection or metabolic disturbance, an EEG, and a brain imaging study. The treatment of a seizure disorder in a person with HD depends on the nature of the seizures. In the juvenile HD patient, myoclonic epilepsy or other generalised seizures may suggest Sodium Valporate as a first treatment choice. Although seizure management in HD is not usually difficult, for the occasional patient seizure control is quite difficult to achieve, requiring multiple medications or specialised referral. More often anti-epileptic medications are used in HD to control mood swings and those typically used are Sodium Valproate, Carbamazepine or Lamotrigine.

SWALLOWING DIFFICULTIES

Dysphagia is, directly or indirectly, the most common cause of death in people with late stage HD, whether through choking, aspiration, or malnutrition. Dysphagia results from impaired voluntary control of the mouth and tongue, impaired respiratory control due to chorea, and impaired judgment, resulting in eating too rapidly, or taking overly large bites of food and gulps of liquid. Dry mouth, which can be brought on by neuroleptics, antidepressants, and anticholinergics, may worsen the problem.

No medications are known to improve swallowing directly. Early referral to a speech-language pathologist will help to identify swallowing difficulties, and periodic reassessment can identify changes in swallowing ability and suggest appropriate non-pharmacologic interventions, such as a change in food consistency. Devices such as enlarged grips for silverware and nonslip plates with raised edges to prevent spilling may prolong independent eating. HD affected individuals should be instructed early in the disease, before the onset of dysphagia, to eat slowly and

deliberately, to sit in an upright position during and after meals, to take small bites, and to clear the mouth of food after each bite by taking sips of liquid.

Table 4: Swallowing tips

- Eat slowly and without distractions.
- Prepare foods with appropriate size and texture.
- Eating may need to be supervised.
- Caregivers should know the Heimlich manoeuvre.

Individuals with dysphagia should avoid doing other activities while eating, in order to concentrate on chewing and swallowing. For instance, patients should not talk while eating, nor be distracted by television or ambient noise. Those who tend to hyperextend the neck due to chorea or dystonia should be encouraged and reminded to use a "chin-tuck" position. Drinking fluid through a straw may be easier than drinking directly from a cup, and the use of a covered cup or mug, like a "sippy cup" used by young children, may prevent spillage due to chorea. Grainy items, such as ground beef or rice, may irritate the pharynx and cause choking. Foods such as steak, which are hard to chew, should also be avoided, or ground to a puree. Patients may have difficulty adjusting to different textures of food, and may do better if they finish each item on the plate in turn.

In late HD, when even liquids may be difficult to swallow, the texture of food should be soft and smooth, and liquids may be thickened with an additive. For those patients who may be unable to follow instructions reliably, a caregiver can cut the food in advance, and ensure that each mouthful has been completely chewed and swallowed before the next bite is begun. Supervision throughout the meal may be necessary, and the family or caregiver should be taught to perform the Heimlich manoeuvre.

In some cases, eating eventually requires so much energy and concentration that the patient becomes tired and frustrated before consuming adequate amounts of food. Weight loss, very prolonged mealtimes or an inability to handle utensils may be the signal that he will need to be fed for at least part of the meal. Self-feeding may be prolonged by having the patient eat more frequent, but smaller meals, and by using "finger foods." The transition to assisted feeding does not have to be all or nothing, as patients may still be able to eat unassisted at certain times and be fed at other times.

Choking may decrease once self-feeding is stopped, because the caregiver will have greater control over the size and frequency of the bites. The caregiver should still promote eating slowly, and not talking while eating, and should make sure the mouth is empty before each bite. With supervision, most patients are able to assist with feeding and to take adequate amounts of food by mouth quite far into the illness.

However, before dysphagia and communication difficulties become severe, the issue of feeding tubes should be discussed with the patient and family, to ensure that appropriate nutrition can be maintained throughout the illness. A gastrostomy tube can clearly improve nutritional status in a debilitated person with severe dysphagia, and may prolong life. However, patients and families may not desire this intervention late in the course of HD. The question of whether to use a gastrostomy tube, and other end of life issues are discussed in the final section of chapter 6.

NUTRITION

The main aims of dietary treatment in HD are to encourage people to achieve a well balanced diet, which includes all the essential nutrients, to prevent or minimise the weight loss frequently seen in the mid to later stages of the disease and to help people regain lost weight where possible.

It has been well documented that many people with HD find it difficult to maintain their body weight and therefore need a higher than normal calorie intake. While the exact reasons for this are unknown, several studies have shown some people have a higher metabolic rate. This is frequently, but not always, associated with increased chorea movements. In the later stages of the disease increasing swallowing problems contribute to weight loss as mealtimes take longer and it can be difficult to ensure a pureed diet provides adequate nutrition.

Maintaining a healthy body weight is essential because people who are underweight (i.e. BMI of less than 18.5) lose muscle mass and therefore feel weaker, become apathetic and depressed, are more prone to catch infections, develop pressure ulcers if their mobility is compromised and take longer to recover from illness, operations or wounds. There is some anecdotal evidence that shows that providing a high calorie intake can help to reduce chorea movements, improve cognition and improve speech & swallowing.

Given the consequences associated with a low BMI it is important to monitor weight on a regular basis, but the frequency will vary from person to person, depending on where they are in the disease process and their weight history. As a guide a someone in the early to mid stages whose weight is stable should be monitored as below:

BMI	> 27	yearly,
BMI	23-26	6 monthly,
BMI	20-23	3 monthly
BMI	18.5 –19	2 monthly
BMI	<18.5	monthly.

When the patient is in the later stages of the disease or if they are losing weight it should be monitored monthly where possible.

Dietary advice

When a patient's BMI is above 23 and stable then it is appropriate to offer general healthy eating advice:

- Aim for a regular meal pattern of 3 meals per day and include starchy foods at each meal.
- Aim for 5 portions of fruit and vegetables per day.
- Include some form of meat, fish, eggs, cheese, pulses or similar foods at least twice a day.
- Aim for 0.5 litre/1 pint of milk per day or it's equivalent in other forms i.e. 75gm milk/3oz cheese or yoghurt.
- If desired include foods containing fats or sugars in moderation as extras to meals.
- Drink 8-10 cups of fluid per day e.g. water, tea, coffee, fruit juice, milk, squash.

Once a patient starts to lose weight or if they are underweight then they need information on how to increase their calorie intake and preferably should be referred to a Registered Dietitian for specialist advice. However if this is not possible then the guidelines below can be followed.

Step one

Gradual weight loss and BMI above 22:

- Encourage a regular meal pattern with high calorie snacks between meals e.g. Cheese and biscuits, sweet biscuits & cakes, sandwiches with fillings such as: cream cheese, peanut butter, jam, thick and creamy yoghurts, mousses, fromage frais.
- Encourage milky drinks e.g. drinking chocolate, fruit smoothies, milkshakes.

- Advise on the use of full fat products e.g. full fat milk, butter rather than reduced fat margarine

Fortify meals by:

- Adding plenty of butter, cheese, evaporated milk, salad cream to potatoes and vegetables
- Use plenty of butter, jam etc on bread, toast, crumpets etc
- Encourage high calorie puddings and add extra cream, evaporated milk, ice cream etc.

Review after 2 months

If weight has stabilised advise patients to maintain changes and continue to monitor weight on a regular basis.

Step 2

If weight loss continues or BMI is less than 22. Advise as above plus introduce supplement drinks.

These can be:

- Either nutritionally complete supplements e.g. Ensure Plus, Fortisip, Clinutren 1.5, Resource Shake, Fresubin.
- Energy which are ready to drink and Complan Shake which needs to be mixed with whole milk. Or milk shake powders e.g. Scandishake, Calshake, and Enshake which need to be made up with whole milk and are not nutritionally complete.

Food supplements are prescribable under the medical card in order to prevent/treat the disease related malnutrition which often occurs in Huntington's Disease.

To ensure compliance and therefore save wastage it is essential to find a supplement that the patient will tolerate. Therefore they should be prescribed a weeks' trial of either 2 nutritionally complete supplements daily or 1 sachet of milk shake powder supplement. Tastes vary from person to person so try a variety of brands until you find one they like which can then be prescribed on a monthly basis, Nutricia and Abbott, who manufacture Fortisip and Ensure Plus respectively, produce variety starter packs of 10-12 cartons, which are useful as an initial prescription.

Step 3

Patients should continue with the supplements until their weight has stabilised and/or they have regained any weight lost. After this they can be gradually reduced but their weight must continue to be monitored closely, particularly if they have swallowing problems and have been recommended to change to a modified texture diet by a Speech and Language Therapist.

Step 4

If a patient continues to lose weight they should be referred to Registered Dietitian as soon as possible as they have the skills, expertise and knowledge of more specialist products, which can be used to prevent further weight loss. They will also be able to discuss issues such as PEG feeding with patients and their carers if required.

In conclusion it is now recognised that nutrition plays an important role in the treatment of HD. Therefore it is essential that all people who are diagnosed with HD should have their weight and dietary intake monitored regularly at the same time as their other symptoms are reviewed. This enables suitable action to be taken as soon as problems appear rather than trying to reverse significant weight loss. It is much easier to prevent weight loss and its consequences than it is to help people to regain lost weight.

DYSARTHRIA

Dysarthria, a difficulty with the physical production of speech, results largely from impairment of voluntary movement. Speech becomes slurred, dysrhythmic, variable in volume due to inconsistent breath support, and increasingly difficult to understand. Furthermore, just as patients do not always appreciate the presence or degree of chorea, some patients do not seem to be aware of distortions in their speech. For others, articulation is a constant source of frustration. No medications are known to be helpful, and dysarthria may be worsened by agents which suppress chorea. However, several interventions may enhance communication in these patients. The listener must do everything possible to promote successful communication, beginning with allowing enough time. Many HD patients thought to be incapable of communication can be understood if the listener is patient enough. Patients may need to be moved to a quieter, calmer environment, and urged to speak slowly. Patients can be asked to spell difficult to understand words. A communication board can also be useful in some cases. A speech-language pathologist may be able to provide additional insights and management strategies.

Dysarthria may be compounded by cognitive problems found in HD, such as word-finding difficulty, difficulty initiating speech, or difficulty completing a sentence. Even those with severe cognitive impairments often respond to cues, such as asking for the size, shape or color of an object.

Even severely impaired patients may be able to respond accurately to a series of yes and no questions. If unsuccessful attempts at communication become very frustrating, it may be better to take a break. The desire for social interaction generally remains, even in those with advanced HD, so strategies for communication should be a priority.

Table 5: Coping strategies for communication

- Allow the person enough time to answer questions.
- Offer cues and prompts to get the person started.
- Give choices. For example, rather than asking "what do you want for dinner?" ask "do you want hamburgers or meatloaf?"
- Break the task or instructions down into small steps.
- If the person is confused, speak more simply and use visual cues to demonstrate what you are saying.
- Ask the person to repeat phrases you did not understand, or spell the words.
- Alphabet boards, yes-no cards, or other communication devices may be helpful.

FALLS

Falls are common in persons with HD, and can be a source of significant morbidity. Usually seen more in the moderate to advanced stages, they often result from the combination of spasticity, rigidity, chorea, and loss of balance. Pharmacotherapy to prevent falls could include treatment of chorea, rigidity, spasticity and dystonia, while minimising the use of drugs such as neuroleptics and benzodiazepines, whose side effects include sedation, ataxia, or parkinsonism. Most efforts at prevention, however, involve not drugs, but modification of the environment and behavior of the patient. Occupational and physical therapists can instruct patients in how to sit, stand, transfer, and walk more safely. Installing handrails in key locations, and minimising the use of stairs can help to reduce falls. Some families convert a ground floor room into a bedroom. Furniture such as tables and desks, particularly items with sharp corners, should be arrayed along the periphery of the room, where they will present less of an obstacle. Floors should be carpeted to lessen the impact when falls do occur. Patients who fall out of bed

may have a mattress placed beside the bed at night, or may sleep on a mattress placed directly on the floor. HD patients will eventually become unable to walk and will need to be transported in a wheelchair. A weighted and padded chair, perhaps with a wedge to keep the hips tilted, or a pommel between the legs, may minimise the chance of a severely choreic or dystonic patient falling or sliding out, or knocking over the chair. Use of a wheelchair is not an all or nothing proposition. Mobility may be extended by using the wheelchair for longer excursions and using other assistive devices such as a walker for shorter distances, or in the home. Walkers with front wheels may be particularly useful when rigidity or loss of balance is a problem. Patients who are particularly prone to falls sometimes wear helmets, or elbow and knee pads to minimise injury. Physical therapy may also help by teaching patients how to minimise injury in a fall and how to get up again after a fall.

GENERAL SAFETY MEASURES

A number of other environmental interventions may reduce the risk of injury. Patients who smoke should do so in a room without flammables, such as rugs, curtains and overstuffed furniture. Patients may need to stop using sharp knives and to switch to microwave cooking to prevent burns and spills. Falls in the bathroom are particularly dangerous, but there are a variety of assistive devices that can be installed. Consultation from a nurse, occupational therapist or physiotherapist may be helpful.

4. THE COGNITIVE DISORDER

INTRODUCTION

The cognitive disorder in HD is considered a "subcortical" syndrome and usually lacks features such as aphasia, amnesia, or agnosia that are associated with dementia of the Alzheimer's type. The most prominent cognitive impairments in HD involve the so-called "executive functions" - abilities such as organisation, regulation and perception. These fundamental abilities can affect performance in many cognitive areas, including speed, reasoning, planning, judgment, decision making, emotional engagement, perseveration, impulse control, temper control, perception, awareness, attention, language, learning, memory and timing.

Several studies have suggested that cognitive and behavioural impairments are greater sources of impaired functioning than the movement disorder in persons with HD, both in the work place and at home. In addition, family members most often report that placement outside the home is initiated because of cognitive and behavioural deterioration rather than motor symptoms.

This chapter provides an overview of cognitive impairments and the related behavior problems that typically accompany HD. In addition, compensation and adaptation strategies are provided, which physicians may recommend to patients, families and other professionals.

DISORGANISATION

Difficulties in planning, organisation, sequencing and prioritising can affect responsibilities at home and at work. Daily tasks, such as attempts to follow a recipe, to maintain a daily planner, to complete a list of household errands, to develop a meeting agenda, or to apply for social security benefits, become daunting.

Many early-stage HD patients complain of problems with organisation and report that they just "can't get things done." There are several ways to compensate for poor organisation, which can be instituted early in the disease. Routines should be established at work or in the home so that the environment can provide structure and organisation. Activities should be organised so that each day is basically the same. For example, 7:00 shower, 7:30 breakfast, 8:00 take bus to work, 8:30 check mail, 9:30 dictate letters, 10:00 coffee, 10:30 staff meeting, 12:00 lunch, 1:00 return phone calls, 2:30 review accounting, 4:00 open meeting to schedule with customers, 5:00 take bus home, 6:00 dinner, 7:00 family time with kids, 8:30 time with spouse, 9:30 read, 10:00 lights out. A central location could be established for posting a daily schedule. Persons who never before used daily planners or computer calendars may need to start. A centralised message center can be used to make lists and organise tasks to be accomplished each day. Additional strategies for dealing with poor organisation are offered in Table 6.

Table 6: Coping strategies for planning and decision making

- Rely on routines, which can be easier to initiate or continue without guidance.
- Make lists which help organise tasks needed to do an activity.
- Prompt each step of an activity with external cues (routine, lists, familiar verbal cues).
- Offer limited choices and avoid open ended questions.
- Use short sentences with 1-2 pieces of information.

LACK OF INITIATION

Some family members complain that the person with HD "just sits around all day and won't do anything." Regulation of behavior involves getting started, maintaining the desired behavior and stopping unwanted behaviors. The initiation, or starting of an activity, conversation or behavior is often compromised in HD. A lack of initiation is often misinterpreted as laziness, apathy or lack of interest, and may be a reason for poor performance at work. Once started, persons with HD may be able to execute the behaviours adequately (i.e., compute taxes, calculate sales, administrate employees, teach school), but may be unable to organise and initiate the behaviours at the appropriate time. External initiation often helps the person with HD remain active and participate in both social and work activities. Keeping a daily routine can minimise the need for internal initiation. Maintaining the desired behavior is usually less of a problem for persons with HD. If this aspect of regulation is impaired, however, the HD patient may be unable to regulate ongoing behaviors in an appropriate manner.

PERSEVERATION

Perseveration, or being fixed on a specific thought or action, can occur when behaviors are inadequately regulated by the brain. Spouses often report that patients become behaviorally rigid, and tend to get stuck on an idea or task. Established routines and gentle reminders of changing tasks can help avoid problems.

An activity that is atypical for the established routine will be particularly stressful and challenging for the person with HD. For instance, travel out of town, or a visit to the doctor or dentist, may disrupt a safe routine. When shifting to a new task, help prepare the person with HD and allow plenty of time for him to adapt to the new idea. There is a delicate balance of how much preparation is needed. Telling of a change in plans too early can cause increased anxiety. Typically, inform the HD patient only one day prior to an event or a few hours before. Allow plenty of time and frequent gentle cues to allow the shift to take place.

IMPULSIVITY

Some persons with HD experience difficulties with impulse control and may develop problem behaviors such as irritability, temper outbursts, sexual promiscuity and acting without thinking. Some degree of impulsivity and dysregulation of behaviors is quite common in HD. Some strategies to help family members and caregivers cope with impulsivity are addressed below.

Table 7: Coping strategies for impulsivity

- Since the person with HD cannot control their responses, a predictable daily schedule can reduce confusion, fear and, as a result, outbursts.
- It is possible that a behavior is a response to something that needs your attention. Don't be too quick to discount it as an outburst.
- Stay calm. This will help you remain able to think and not react emotionally and impulsively yourself. In addition, staying calm may help the person calm down.
- Let the person know that yelling is not the best way to get your attention and offer alternative methods for getting your attention.
- Remember, although the things being said are hurtful or embarrassing, generally the person is not doing this intentionally. This is the HD talking, not your loved one.
- The person may be remorseful afterward. Be sensitive to his efforts to apologise.
- Do not badger the person after the fact. It won't help. Remember, this lack of control, likely, is not by choice.
- Medications may be helpful for outbursts and sexually inappropriate behavior. Talk to your physician.

IRRITABILITY AND TEMPER OUTBURSTS

One of the most typical complaints we hear from HD families is concern about irritability and temper outbursts. These signs can be present for a couple of reasons. First, it is important to assess for depression when increased irritability is reported. Oftentimes, irritability and temper outbursts diminish when a mood disorder is treated. Many times, however, irritability or outbursts remain even in the absence of a mood disorder.

Examination of the underlying causes of irritability and temper outbursts is helpful in diminishing the frequency and severity of these behaviors. Persons with HD are continually challenged by previously routine tasks or activities that are experienced as overwhelming. HD results in a progressive loss of abilities that often "sneak up" on persons with HD. Several patients have confided that "I didn't realise I could no longer do it." Close attention should be paid to the signals, verbal or nonverbal, that the patient is upset or wanting something, so that they do not get to the stage of exploding before they receive attention.

Knowledge of the person and sensitivity to his needs means that some situations can be anticipated and potential frustration defused. It may be possible to identify situations which trigger frustration and either avoid them or provide diversional activities. An awareness of the person's capabilities is very important, so that he is encouraged to be as independent as possible and allowed to take risks without risking constant exposure to failure.

Although this encouragement to maintain independence is not always possible at work, it is critical to encourage in the home. The person with HD should be encouraged to do things for himself and to participate in primary decision-making as long as possible, except perhaps in situations where safety is an issue (i.e. driving or cooking). Family members should be responsible for providing a safe environment so that no person is ever in danger. Remove dangerous implements, such as guns, from the house and have emergency numbers near the telephone.

Listed overleaf are some general strategies for families to employ to minimise irritability and some coping skills for temper outbursts.

PERCEPTUAL PROBLEMS

HD causes deficits in spatial perception. The mental manipulation of personal space is impaired, even early in the disease. For instance, the judgment of where the body is in relation to walls, corners or tables may be disturbed, resulting in falls and accidents. Precautions might include carpeting the floors and removing furniture with sharp corners to the periphery of the room, where it will be out of the patient's path. Behavior problems reported by family members are often due to another kind of impaired perception, unawareness of changes due to HD, which can lead to challenges in providing care.

Table 8: Coping strategies for irritability and temper outbursts

- Assess your own expectations regarding the HD affected individual. A family member may be unwilling or unable to accept the patient's new limitations.
- Try to keep the environment as calm and controlled as possible.
- Speak in a low, soft voice. Avoid confrontations and ultimatums. Sit down and keep hand gestures quiet.
- Try to identify circumstances which trigger irritability and temper outbursts and avoid them.
- Redirect the HD person away from the source of anger.
- Learn to respond diplomatically, acknowledging the patient's irritability as a symptom of frustration.

UNAWARENESS

Denial is commonly considered a psychological inability to cope with distressing circumstances. We often see this in situations such as the loss of a loved one, a terminal disease, or a serious injury. This type of denial typically recedes over time as the individual begins to accept their losses. Individuals with HD often suffer from a more recalcitrant lack of insight or self-awareness. They may be unable to recognise their own disabilities or evaluate their own behavior. This type of denial is thought to result from a disruption of the pathways between the frontal regions and the basal ganglia. It is sometimes called "organic

denial," or anosognosia, and is a condition that may last a lifetime. We recommend that "unawareness" be used to describe this type of denial in HD to distinguish it from the more familiar kind and to avoid thinking of patients with HD as suffering from a purely psychological problem.

Unawareness often plays a significant role in seemingly irrational behavior. At first unawareness may be beneficial because it keeps the individual motivated to try things and to avoid labeling himself. In this way it may prevent demoralisation. On the other hand, unawareness may lead to anger and frustration when the individual cannot understand why he cannot work or live independently. The HD patient with unawareness sometimes feels that people are unjustifiably keeping him away from activities that he could do, such as driving, working, or caring for children, and may attempt to do these things against the advice of family and friends. This type of unawareness can become dangerous.

Table 9: Coping strategies for unawareness

- Do not make insight the central goal. A person may be able to talk about his problems without acknowledging having HD.
- Unawareness will not always respond to interventions, and a person with HD may never seem to "accept" the disease.
- Counselling may help someone with HD come to terms with the diagnosis but may have little impact on specific insight.
- It may be helpful to develop a contract, even a formal written agreement, that includes incentives for compliance but "sidesteps" the awareness issues.

Organic denial is also an issue for health professionals, friends, and family members, who may delay making the diagnosis or keep the diagnosis from the affected individual because they are concerned that he "cannot handle it." Some people interpret the unawareness as a sign that the individual does not want to know. We have not found that talking about HD to a person with unawareness will cause negative consequences. In our clinical experience, organic denial is not easily amenable to treatment or change. Nevertheless, there are different degrees of unawareness. It may be that the person can talk about her problems, but not acknowledge that she has HD.

In such a case, one might try to address the problems while avoiding discussion of the diagnosis. Noncompliance with therapy or nursing care should not automatically be interpreted as intentional. It may be helpful to develop a contract that includes incentives for compliance. Denial can thus be sidestepped, while behavioural goals remain the same. For example, the goal may be to convince an unsafe driver to stop, rather than to accept the diagnosis, or acknowledge why he must stop driving.

ATTENTION

There are many different types of attention. In persons with HD, simple attention often remains intact. In contrast, sustained or complex types of attention become impaired by HD. For instance, most persons with HD will experience difficulty with what is called "divided attention," or the capacity to do two things at once. For most people, divided attention is impaired when we are tired, sick, or stressed. In HD, divided attention is compromised most of the time, regardless of extra stress. Consequently, a person may complain that he can't "pay attention" as well as he used to.

Divided attention is needed to drive a car while listening to the radio, talking to the kids in the back seat, or talking on the cell phone. When divided attention is impaired it is recommended that patients try to do only one thing at a time. For instance, an HD-affected person should turn off radios, television, and telephones, and limit conversations while cooking dinner. When swallowing becomes a problem, mealtime distractions should be minimised and the patient should concentrate on chewing and swallowing to limit choking.

LANGUAGE

Communication, or the transfer of information from one person to another, requires a complex integration of thought, muscle control, and breathing. HD can impair all three of these functions. There are two main aspects to communication: getting the information IN (understanding) and getting the information OUT (talking). Both of these aspects can be impaired by HD, making communication a difficult task.

The most prominent language difficulties in people with HD are (1) speaking clearly (articulation), (2) starting conversation (initiation), and (3) organising what's coming in and going out.

Misarticulation

Motor speech impairments are quite typical in HD. Persons with HD have even been accused of being drunk due to their sluggish speech articulation. A lack of motor coordination causes difficulties with enunciation and the breath control underlying speech.

Impaired initiation of speech

Word finding is often impaired, while knowledge of vocabulary is retained, because it takes the brain much longer to search and retrieve the desired object. Listeners sometimes fail to wait long enough for the brain to do its job.

In addition to speed limitations, the brain fails to regulate the sequence and amount of traveling information, resulting in impairments in starting and stopping. When language initiation is compromised by HD, techniques such as phrasing questions with alternate choice answers (e.g., yes or no; lasagna or spaghetti) may help someone get started or retrieve the desired response.

Disorganisation of language content

In contrast to the basic impairments in language output, the basic capacity to understand language remains relatively intact in HD. Even in later stages of the disease, language comprehension may remain when the ability to speak is significantly diminished. This fact is important to communicate to family members, staff at care facilities and other professionals involved. Even if a patient cannot express herself, it is likely that she can understand what is being said. Difficulties with word usage are rare in persons with HD, as are frank aphasia or impairments in semantic memory. The trouble that occurs in persons with HD is an inability to organise the outgoing and incoming language, resulting in miscommunication. To aid the person with HD in organising language output and input it is best to rely on short simple sentences and to assess understanding frequently during important conversations.

LEARNING AND MEMORY

The type of memory impairments found in HD consist mostly of difficulties in learning new information, and in retrieving acquired information, but not in storage of information. Problems occur in getting information in and out, due to the slowed speed of processing and the poor organisation of information. Several studies have found that HD patients can demonstrate normal memory for information if offered in a recognition format.

If, rather than asking "can you tell me what time your doctor's appointment is today?," one inquires "is your doctor's appointment at 10:00 or 11:00 today?," persons with HD can often answer correctly. Similarly, if patients with HD are given a long list of words to learn and are required to say the words back freely they perform poorly. But if they are given a list of words and asked to recognise which ones were on the earlier list they demonstrate good memory.

It has been observed that persons with severe amnesia such as that associated with Korsakoff's syndrome, herpes encephalitis, or Alzheimer's disease can experience defective explicit memory, such as for names and dates, and intact implicit, or unconscious memory, such as the ability to tie one's shoes. In contrast, persons with HD typically have impairments in skills that depend on implicit memory. Driving, playing a musical instrument, or riding a bike are all motor memories that can be considered implicit, or unconscious. HD impairs this motor memory system, making HD sufferers reliant on more effortful conscious memory systems to drive a car. Consequently, driving will take much more concentration and effort, resulting in increased fatigue and irritability.

Table 10: Coping strategies for memory

- Keep day to day activities as routine as possible.
- Use schedules.
- Use "to do" lists and reminders.
- Offer a list of choices to assist with recall.
- Provide cues to help with the retrieval of information.

TIMING

Some recent findings have suggested that persons with HD have difficulty with the estimation of time. For instance, persons with HD may be less able to judge how much time has elapsed. Spouses often complain that their once-punctual spouse becomes frequently late and mis-estimates how long activities will take. Frequent reminders may be needed to keep on schedule. It is helpful to allow extra time and avoid time pressure when possible.

THE PROGRESSION OF COGNITIVE IMPAIRMENTS

Although performance in IQ tests often remains within the normal range in the early stages of the disease, cognitive deficits are evident in speed of processing, cognitive flexibility (or the ability to shift topics readily)

and the organisation of complex information. The most sensitive indicator of early HD on the Mini-Mental State Examination is serial sevens (the ability to subtract 7 from 100 serially) and the most sensitive subscale on the Mattis Dementia Rating Scale is initiation (the ability to begin and maintain verbal and motor behaviors).

There exist few longitudinal studies of the cognitive decline in HD. Based upon the information available, speed, organisation, and initiation of behavior are impaired in early HD, constructional impairments worsen in mid-stage HD, and some abilities remain relatively spared (memory, language comprehension) even in the later stages of the disease. Clinically, as the disease progresses, the severity of cognitive impairments increases and patients are often unable to speak or communicate their views in late stages.

5. THE PSYCHIATRIC DISORDER

INTRODUCTION

Patients with Huntington's disease who have psychiatric disorders generally suffer from underdiagnosis and undertreatment. It is important to remember that psychiatric problems, particularly depression, are very common and very devastating in HD, but they are also very treatable. Relieving a depression in someone with HD may be the single most effective intervention a physician can perform.

Psychiatric disturbances in HD are varied. Some patients suffer from conditions such as Major Depression, Bipolar Disorder, or Obsessive-Compulsive Disorder which are specific well-described syndromes, found in all sorts of patients. Many, if not most people with HD also experience less well defined, non-specific changes in personality and mood, such as irritability, apathy, or disinhibition. Most of these psychiatric problems are believed to be related directly to the central nervous system injury caused by HD. This issue is discussed further in the chapter on cognition.

SPECIFIC PSYCHIATRIC DIAGNOSES

Depression

"Who wouldn't be depressed if they had HD?" Research and clinical experience shows that many HD patients are not depressed, and able to adapt gradually to having HD.

Nonetheless, even severe depression in someone with HD is often explained away as an “understandable” reaction, therefore not requiring additional treatment. This potential for overinterpretation exists in a variety of other serious medical conditions such as AIDS, stroke, and Alzheimer’s disease, which have a high comorbidity with depression. In fact, those patients who have a depressive syndrome, even when the depression is “understandable,” and even when there are clear triggers, usually respond to standard treatments, including medications and psychotherapy. Because depression in HD appears directly related to the brain disease, pharmacotherapy is usually indicated.

Table 11: Signs and symptoms of depression

- Depressed or irritable mood
- Loss of interest or pleasure in activities
- Change in appetite, or weight loss
- Insomnia or hypersomnia
- Loss of energy
- Feelings of worthlessness or guilt
- Impaired concentration
- Thoughts of death or suicide
- Loss of libido
- Feelings of hopelessness
- Social withdrawal
- Psychomotor retardation or agitation

(Based on DSM-IV criteria)

Major Depression is a clinical syndrome, a constellation of signs and symptoms which, taken together, suggest the diagnosis. Use of diagnostic criteria helps to distinguish major depression from demoralisation, transient changes in mood caused by negative life events, such as bereavement, and from some of the symptoms of HD itself, such as weight loss, trouble with concentration, and apathy. Patients with Major Depression have a sustained low mood, often accompanied by changes in self-attitude, such as feelings of worthlessness or guilt, a loss of interest or pleasure in activities, changes in sleep, particularly early morning awakening, and appetite, loss of energy, and hopelessness. Depressed patients often feel worse in the morning than in the afternoon.

In severe cases of depression, patients may have delusions or hallucinations, which tend to match their depressed mood. A patient may hear voices berating him or urging him to commit suicide, or may have the delusion that he

will be going to jail, or that he has killed his family.

Depressed patients often display psychomotor retardation, a slowing of speech and movement as a result of depression. In extreme cases they can appear stuporous or catatonic.

It is important to remember that because depression is a syndrome, with various symptoms and manifestations, the presenting complaint may be something other than a low mood. For example a depressed patient may complain of insomnia, anxiety, or pain, with each problem only a symptom of the depression which is the underlying cause. It is vital to get the whole story, because symptomatic treatment for any of these complaints, e.g. sleeping pills, tranquilisers, or narcotics, could be worse than no treatment at all.

A specific complaint of depressed mood is not necessary to make the diagnosis if the patient has the other symptoms. In fact patients with HD often have trouble identifying or describing their emotional state. Depression in such a patient may be characterised by changes in sleep or appetite patterns, agitation, tearfulness, or a drop-off in functional abilities. In such circumstances the diagnosis should be considered.

In evaluating an HD patient with depression the physician also needs to consider whether some physical problem, other than HD, might be the cause. The patient’s medical history should be reviewed for conditions such as hypothyroidism, stroke, or exposure to certain drugs associated with mood changes, such as steroids, reserpine, beta-blockers, and particularly alcohol.

Pharmacotherapy of depression

Depressed people with HD can usually be treated with the same agents as any other patient with depression, but certain factors may make some drugs easier to use. Many new medications have become available since the first edition of the Physician’s Guide and the tricyclic antidepressants, while highly effective, should no longer be considered the standard first-line choice. Instead, the physician should consider the Selective Serotonin Re-uptake Inhibitors (SSRIs) such as sertraline (Zoloft), paroxetine (Seroxat), fluoxetine (Prozac), Citalopram (Ciprimil) and fluvoxamine (Faverin). These offer the advantages of low side effect profile, once-a-day dosing, and safety in the event of overdose. Of these drugs, fluoxetine has a much longer half-life. If a patient develops an unpleasant side effect it will take longer to wear off. On the other hand this may make it a good choice for patients who sometimes forget to take their medicine.

Table 12: Key points in the treatment of depression

- Avoid overinterpretation of symptoms.
- Depression is very common in HD. Have a low threshold for diagnosis and treatment.
- HD patients are sensitive to side effects. Start medications at a low dose and increase gradually.
- Ask about substance abuse.
- Ask about suicide.

The SSRIs are sometimes stimulating and most patients should take them in the morning rather than at bedtime. Initial side effects may be GI upset or diarrhoea, and increased anxiety or insomnia (although, if they are part of a depression, these symptoms will eventually respond to the treatment). SSRI-induced insomnia may respond to 25-50mg of trazodone at night (Molipaxin). A small number of patients will develop sexual problems on SSRIs, particularly anorgasmia or ejaculatory delay. These symptoms are highly dependent on the dose. Some people have asserted that SSRIs, particularly fluoxetine, cause violence or suicide in psychiatric patients. There is no valid evidence to support this claim. Citalopram has a shorter half life than Fluoxetine and less drug interactions.

Patients with HD are sensitive to the potential side effects of CNS drugs. Any new drug should be started carefully, and increased gradually. Sertraline 25-50mg, paroxetine 10mg, Citalopram 10mg or fluoxetine 10mg are appropriate starting doses. If well tolerated, the dose can be increased after a few days or a week to sertraline 50-100mg, paroxetine 20mg, Citalopram 20mg or fluoxetine 20mg. Most patients will respond to these doses, but sometimes higher doses will be necessary. As we will discuss, SSRIs may also be particularly useful for some of the more nonspecific psychiatric symptoms found in patients with HD, such as irritability, apathy, and obsessiveness.

Other, newer antidepressants we have used with success in patients with HD include bupropion (Wellbutrin), venlafaxine (Effexor), and nefazodone (Dutonin). These all require dosing several times a day. A new formulation of venlafaxine, Effexor XR, may be given once a day, and nefazodone is sometimes given in a single bedtime dose, despite the short half-life. It is often difficult for depressed patients, especially those with cognitive impairment, to adhere to a complex medication regimen. Therefore these drugs may not be good first choices if there is no responsible family member who will help make sure that the patient takes his medicine.

Table 13: Medications used to treat depression

Class	Medication	Starting dose	Maximum dose	Adverse effects
SSRIs	Fluoxetine	10-20mg	60-80mg	Insomnia, diarrhea, GI upset, restlessness, weight loss
	Sertraline	25-50mg	200mg	Similar
	Citalopram	10-20mg	60mg	Similar
	Paroxetine	10-20mg	40-60mg	Similar, more sedation
Tricyclics	Nortriptyline	10-25mg	150-200mg	Dry mouth, blurry vision, constipation, hypotension, tachycardia, sedation
Other	Nefazodone	50-100mg	450-600	Sedation, nausea, dry mouth, dizziness, constipation
	Bupropion	100-200mg	300-450mg	Seizures, agitation, dry mouth, insomnia, nausea
	Venlafaxine	25-37.5mg	225mg	Hypertension, nausea, headache, constipation

Tricyclic antidepressants (TCA's) are much less frequently used because of their side effect profile and the dangers of over dosage. They can be given once a day (usually at bedtime because of sedative properties). Common side effects of TCA's include constipation, dry mouth, tachycardia, and orthostasis. We tend to favor nortriptyline over the others because of the relatively low incidence of these side effects and because of the well-established range of blood levels which have been associated with efficacy. It is not necessary to reach the target blood level if the patient has already responded to a lower dose, but the availability of meaningful blood levels for the TCA's can serve as a useful check of compliance, and a reassurance that a patient's dose is optimal.

Since TCA's can worsen conduction delays, an ECG is indicated prior to treatment if the patient's cardiac status is unknown. TCA's are **extremely** dangerous in overdose. As little as a week's supply may be fatal if taken at once. They are a poor choice in patients with a history of deliberate overdoses and may have to be dispensed only a few pills at a time if this is a concern.

If the patient's depression is accompanied by delusions, hallucinations, or significant agitation, it may be necessary to add an antipsychotic medication to the regimen, preferably in low doses to minimise the risk of sedation, rigidity, or parkinsonism. If the neuroleptic is being used for a purely psychiatric purpose, and is not required for suppression of chorea, the physician may want to prescribe one of the newer agents such as risperidone (Risperdal), olanzapine (Zyprexa), or quetiapine (Seroquel). These drugs may have a lower incidence of side effects and appear to be just as effective. Among the older neuroleptics, high potency agents such as haloperidol (Haldol) or fluphenazine (Modicate) tend to be less sedating, but cause more parkinsonism. Lower potency agents such as thioridazine (Mellaril) may aid with overactivity and sleeplessness, but tend to be constipating and can cause orthostasis and cardiac dysrhythmias.

Benzodiazepines, particularly short acting drugs such as lorazepam (Ativan) may be another good choice for the short-term management of agitation. In any case neuroleptics and benzodiazepines used for acute agitation should be tapered as soon as the clinical picture allows.

Electroconvulsive therapy (ECT) has also been found effective in depressed patients with HD. This treatment should be considered if a patient does not respond to

several good trials of medication, or if an immediate intervention is needed for reasons of safety. For example a severely depressed patient may be refusing food and fluids, or may be very actively suicidal. ECT may be particularly effective in treating delusional depression.

Depressed patients should always be asked about substance abuse. Substance abuse, particularly of alcohol, can be both a consequence or a cause of depression, makes treatment difficult or impossible if not addressed, and significantly increases the risk of suicide.

Suicide

Depressed patients should always be asked about suicide, and this should be regularly reassessed. It is a misconception that suicidal patients will not admit to these feelings. The question should be asked in a non-intimidating, matter-of-fact way, such as "have you been feeling so bad that you sometimes think life isn't worth living?" Or, "have you even thought about suicide?"

If the patient acknowledges these feelings, the clinician needs to ask more questions to evaluate their severity and decide on the best course of action. Are the feelings just a passive wish to die or has the patient actually thought out a specific suicidal plan? Does the patient have the means to commit suicide? Has she prepared for a suicide, such as by loading a gun or hoarding pills? Can the patient identify any factors which are preventing her from killing herself? What social supports are present? Some patients, although having suicidal thoughts, may be at low risk if they have a good relationship with their doctor, have family support, and have no specific plans. Others may be so dangerous to themselves that they require emergent hospitalisation.

Although there have been cases of non-depressed patients with HD harboring chronic suicidal feelings, we feel that most, if not all, suicidal patients with HD suffer from Major Depression and can be treated successfully. So as not to miss such cases, it is helpful to think of all patients with HD who are suicidal as depressed until proven otherwise. If the clinician is unsure, the patient should be treated presumptively. This is not to say that a person with HD, particularly early in the course of the disease may not express a fear of becoming helpless one day, or a desire not to live past a certain degree of impairment. A physician should listen supportively to these concerns, realising that most patients will be able to adapt if they are not suffering from depression.

Table 14: Some antipsychotic medications used in HD

Medication	Starting dose	Maximum dose	Side effects
Fluphenazine	0.5-2.5mg	20-30mg	Sedation, parkinsonism, dystonia, akathisia, hypotension, constipation, dry mouth, weight gain
Haloperidol	0.5-2.5mg	20-30mg	same
Risperidone	0.5-1mg	4-6mg	less parkinsonism, less dystonia
Olanzapine	2.5-5mg	15-20mg	less parkinsonism, less dystonia
Quetiapine	25-50mg	500-750mg	less parkinsonism, less dystonia

Mania

While depression is the most common psychiatric problem in HD, a smaller number of patients will become manic, displaying elevated or irritable mood, overactivity, decreased need for sleep, impulsiveness, and grandiosity. Some may alternate between spells of depression and spells of mania with times of normal mood in between, a condition known as bipolar disorder. Patients with these conditions are usually treated with a mood stabiliser.

Lithium is probably still the most popular mood stabiliser for people with idiopathic bipolar disorder, but we have not found it to be as helpful in patients with HD. It is not known why this is the case. Lithium has a narrow therapeutic range, particularly in patients whose food and fluid intake may be irregular, but there may be some other aspect to the mood disorders found in HD patients which make them poor lithium responders.

We recommend beginning with the anticonvulsant Sodium Valproate (Epilim) or valproic acid (Depekene) at a low dose such as 125 to 250mg pc bid and gradually increasing to efficacy, or to reach a blood level of 50-150mcg/ml. A dose of 500mg pc bid is fairly typical, but some patients will require as much as several grams per day. Another anticonvulsant, carbamazepine (Tegretol),

is also an effective mood stabiliser. This can be started at 100-200mg per day, and gradually increased by 100mg/day to reach an effect or a therapeutic level of 5-12mcg/ml, which may require a dose of 800-1200mg/day. Therapeutic ranges for these drugs were established on the basis of their anticonvulsant properties, so it is important to remember that a patient may show a good psychiatric response below the minimum "therapeutic" level (but generally should not exceed the maximum level in any case). Both drugs carry a small risk of liver function abnormalities (particularly sodium valproate) and blood dyscrasias (particularly carbamazepine), and so LFT's, and CBC should be routinely monitored every few months and clinicians should be alert for suggestive symptoms. Valproic acid may cause thrombocytopenia, and both drugs are associated with neural tube defects when used during pregnancy.

Manic patients with HD who have delusions and hallucinations may require a neuroleptic, and patients who are very agitated may need a neuroleptic or a benzodiazepine for immediate control of these symptoms. As discussed for depression, the doctor may wish to prescribe one of the newer antipsychotics which have fewer parkinsonian side effects, such as risperidone, olanzapine, or quetiapine.

Table15: Medications used for mania in HD

Medication	Starting dose	Maximum dose	Side effects
Neuroleptics (see table 14)	See table	See table	See table
Sodium Valproate	250mg	500-2000mg	G.I. upset, sedation, tremor, liver toxicity, throbocytopenia
Carbamazepine	100-200mg	1200-1600mg	Sedation, dizziness, ataxia, rash, bone marrow suppression

In cases of extreme agitation, a rapidly acting injectable agent, such as lorazepam may be necessary. Finally, ECT is known to be a very effective treatment for idiopathic mania and should be considered when other treatments fail, or when the individual is extremely dangerous.

Obsessive-compulsive disorders

Obsessions are recurrent, intrusive thoughts or impulses which are experienced as being senseless, at least initially. A compulsion is a repetitive performance of the same activity, a stereotyped routine which must be followed, often in response to an obsession, such as handwashing because of an obsessive concern with germs. Obsessions are usually a source of anxiety and the patient may struggle to put them aside, whereas the acting out of compulsions generally relieves anxiety and may not be as strongly resisted.

True Obsessive-Compulsive Disorder (OCD) is rare in HD, but HD patients often display an obsessive preoccupation with particular ideas. Patients may worry about germs or contamination, or engage in excessive checking of switches or locks. Sometimes patients will become fixated on an episode of being wronged in the past (e.g. fired from a job, divorced, driver's license revoked), and then bring it up constantly, or become preoccupied with some perceived need, such as a desire to go shopping, or to eat a certain food.

Serotonergic antidepressants are used to treat OCD and may ameliorate obsessions and compulsions in HD patients that do not meet the criteria for the full syndrome. The use of the tricyclic antidepressant clomipramine (Anafranil) has largely been superseded by the SSRIs fluoxetine, sertraline, paroxetine and fluvoxamine which have milder side effects and lower lethality in overdose. Patients may require higher doses than those needed for depression, e.g. 40-60mg of fluoxetine. For relentless perseverative behavior unresponsive to these agents, one might consider neuroleptics, keeping in mind that the newer, atypical drugs may be better tolerated.

Schizophrenia-like disorders

Schizophrenia and schizophrenia-like conditions are much less common than affective disorder in HD. The new onset of delusions and hallucinations should prompt a search for specific causes or precipitating factors, including mood disorders, delirium related to metabolic or neurologic derangements and intoxication with or withdrawal from illicit or prescription drugs.

Once these possibilities of mood disorder, drug intoxication, and delirium have been considered, neuroleptics may be employed for HD patients with schizophrenia-like syndromes. The doses used for treatment of psychosis may be somewhat higher than those used for treatment of chorea. As mentioned before, if neuroleptics are not needed for the control of involuntary movements, patients may do better on newer agents such as risperidone, olanzapine or quetiapine which do not cause as many extrapyramidal side effects. Some patients will respond completely and others only partly, reporting that "voices" have been reduced to a mumble, or becoming less preoccupied with delusional concerns. Patients with delusions will rarely respond to being argued with, but a clinician may certainly express skepticism regarding a delusional belief and explain to the patient that it may be the product of a mental illness. Caregivers should be encouraged to respond diplomatically, to appreciate that the delusions are symptoms of a disease, and to avoid direct confrontation if the issue is not crucial.

Delirium

Delirium, an abnormal change in a patient's level of consciousness, may result from a variety of toxic, structural or metabolic causes. Delirious patients may have waxing and waning of consciousness, may be agitated or lethargic, and frequently have disturbed sleep. Patients in the later stages of HD, are particularly vulnerable to delirium. Common causes of delirium in HD include prescription medications, particularly benzodiazepines and anticholinergic agents, alcohol or illicit drugs, and medical problems such as dehydration and respiratory or urinary tract infections. It is important to ask about over the counter medicines such as cold tablets and sleep aids, which patients and families may forget to mention. Subdural hematoma, due to a recognised or unrecognised fall should also be considered if the patient suffers a sudden change in mental status. Delirium can also come about gradually as an underlying problem worsens. For example, a dehydrated patient may no longer be able to tolerate his usual medication regimen. Delirium can also be mistaken for a number of other conditions in HD. As mentioned previously, it may be accompanied by hallucinations or paranoia. Clinicians usually expect delirious patients to exhibit agitation or hyperarousal and may overlook the delirious patient who is somnolent or obtunded. Such patients may seem depressed to their families, but when questioned will not report a low mood.

Physicians should consider a diagnosis of delirium whenever confronted with an acute behavioural change in someone with HD and should review the medication list, examine the patient, and obtain necessary laboratory studies, including a toxicology screen if indicated. Identification and correction of the underlying cause is the definitive treatment for delirium. Low doses of neuroleptics may be helpful in managing the agitation of a delirious patient temporarily.

PSYCHIATRIC SYMPTOMS NOT BELONGING TO A SPECIFIC DIAGNOSTIC CATEGORY

Patients with Huntington's disease may suffer from a variety of emotional symptoms which do not fit any specific psychiatric diagnosis, but may nevertheless be a source of distress and a focus of treatment including irritability, anxiety and apathy. Some of these symptoms are related to the disease itself, and others can be seen as a response to changing circumstances, such as a patient who becomes anxious about going to the market because her involuntary movements attract attention. Patients with HD may undergo personality changes, becoming irritable, disinhibited, or obsessional. In some cases these changes represent an accentuation, or coarsening of personality characteristics the person already had. Other times they will be a radical departure from the patient's usual state, which can be very distressing to families. Families should be reassured, as patients can usually be helped by better communication, environmental interventions, and judicious use of medications.

Irritability

Irritability is a common complaint from persons with HD and their families. It is often associated with a depressed mood, but may also result from a loss of the ability of the brain to regulate the experience and expression of emotion. Irritability in persons with HD may take the form of an increase in the patients' baseline level of irritability, or there may be episodes of explosiveness as irritable responses to life events become exaggerated in intensity and duration. Other patients may not be irritable under most circumstances, but will develop a kind of rigidity of thinking which will cause them to persevere relentlessly on a particular desire or idea, becoming progressively more irritable if their demands are not met. One woman, for example, insists on having ten or twelve varieties of juice in the refrigerator at all times and was markedly irritable during a recent visit to the clinic. Her husband

had started the car to drive to the clinic and had refused to go back into the house to get her another glass of juice. Hours later she was still dwelling on it and kept interrupting the interview to say that she wanted to go home to have a drink.

Irritability in HD may have a variety of triggers and exacerbating causes. It is important to understand it in context and avoid premature use of medications. One must first understand exactly what the informant means by saying the patient is irritable or agitated. Does the patient appear restless? Is the patient yelling or verbally abusive? Is there potential for violence? Many factors can precipitate an irritable episode, such as hunger, pain, inability to communicate, frustration with failing capabilities, boredom, and changes in expected routine. Family members and caregivers should learn to respond diplomatically, appreciating the patient's irritability as a symptom. Confrontations and ultimatums should be avoided if the issue is not crucial. The beta blocker Propranolol can reduce irritability in relatively low doses (20mg-40mgs). At higher doses it can lead to or exacerbate depression.

The environment should be made as calm and structured as possible. Some families achieve this more easily than others. Family settings in which there are children and adolescents, unpredictable working hours, noise, or general chaos may lead to irritability and aggressiveness in persons with HD. Pointing caregivers in the direction of the voluntary organisations, such as the Huntington's Disease Association of Ireland, can provide emotional support and are a forum for sharing strategies that members have found useful in their own households.

When irritability is severe, or enduring, or is expressed physically, patients are often described as agitated. A great deal of overtreatment, particularly with neuroleptics, stems from **continuous** use of a drug for an **episodic** problem. It is always necessary to revisit the situation and see whether the drug has actually reduced the frequency of outbursts. For episodic outbursts, success often results from combining drug therapy with a careful analysis of the context and precipitants of the outburst. Nevertheless, we have found a number of medications helpful in treating enduring irritability. Patients may respond to antidepressants, particularly the SSRIs (sertraline, fluoxetine, and paroxetine) even if they do not meet all the criteria for major depression.

Table 16: Coping strategies for irritability

- Restructure the person's expectations and responsibilities to manage frustration. The environment should be as calm and structured as possible.
- Respond diplomatically, acknowledging the irritability as a symptom. Confrontations and ultimatums should be avoided unless the issue is crucial.
- Try to identify circumstances which trigger temper outbursts, and redirect the person away from the source of anger.
- Family and caretaker support groups can provide valuable emotional support and are good places to learn and share effective strategies.

The optimal doses for treating irritability are not known but one should start at a low dose and increase gradually as in the treatment of depression (see table 13). These agents may be particularly useful when the irritability seems tied to obsessions and perseveration on a particular topic. As in the treatment of depression, improvement may not occur for several weeks. Mood stabilisers such as sodium valproate and carbamazepine have also been helpful and could be administered as outlined for bipolar disorder (see table 15).

Low dose neuroleptics may be helpful, particularly the newer, "atypical" ones which have fewer side effects. Long-acting benzodiazepines, such as clonazepam (Rivotril), starting at low doses, e.g. 0.5mg/day, have also been helpful. The clinician must carefully monitor patients treated with these agents, as overdosing can lead to falls or aspiration.

Apathy

Apathy is common in HD and is probably related to frontal lobe dysfunction. Apathetic patients become unmotivated and uninterested in their surroundings. They lose enthusiasm and spontaneity. Performance at work or school becomes sluggish. The symptom of apathy can be very troubling to families, if they see the active person they knew slipping away. It can be a source of conflict for caregivers, who know the person is physically capable of activities but "won't" do them.

Families need much education and support in this regard and should learn to practice a combination of exhortation and accommodation. While apathetic patients have trouble initiating actions, they will often participate if

someone else suggests an activity and works along with them to sustain energy and attention. For example, a man with HD had always loved fishing, but when his brother came to take him fishing for his birthday he wanted to stay home in front of the television. The brother insisted, and when they left the house, he had a good time fishing all day. When he returned, he immediately turned the television back on.

Table 17: Coping strategies for apathy

- Use calendars, schedules and routines to keep the person busy.
- Do not interpret lack of activity as "laziness."
- Patients may not be able to initiate activities, but may participate if encouraged by others.
- Gently guide behaviors, but accept "no."

Apathy can be hard to distinguish from depression. Apathetic patients, like those with depression, may be sluggish, quiet, and disengaged. They may talk slowly, or not at all. By and large apathetic patients will deny being sad, but in distinguishing the two it is important to ask not only about the patient's mood, but about other depressive symptoms as well, such as a change in sleeping or eating patterns, feelings of guilt, or suicidal thoughts. Neuroleptics and benzodiazepines can cause or worsen apathy. The need for these medications should be reexamined if the patient is apathetic.

Depressed patients with apathy should be treated aggressively for their depression, which may cause the other symptoms to remit. It can be very difficult to distinguish depression from primary apathy, but patients with primary apathy sometimes respond to psychostimulants such as methylphenidate (Ritalin) or dextroamphetamine (Dexedrine). These medicines are highly abusable and may exacerbate irritability and chorea. They should be used with caution. It may be more prudent to make a trial of a non-sedating antidepressant, such as an SSRI, first even if the patient does not seem to meet the criteria for depression, as these agents have also occasionally been helpful.

Anxiety

Patients with HD are vulnerable to anxiety because of life circumstances, but also because of physical changes in the brain. Patients may develop a social phobia related to embarrassment about visible symptoms.

As thought processes become less flexible, patients may be made anxious by trivial departures from the usual routine. Patients may worry for days in advance about what to wear when going to the hairdresser or whether to attend a family function.

In addressing anxiety, attempts should be made to decrease the complexity of the patient's environment. Stopping a job that has become too difficult may result in a remarkable decline in symptoms. Assisting the caregiver in establishing a predictable routine for the patient is helpful. Some caregivers find it useful to refrain from discussing any special events until the day before they are to occur. Patients who are very fearful of going to the doctor may need to be told only that they are going on an errand until they reach the clinic.

Some patients will not improve with counselling and environmental interventions and will require pharmacotherapy. The clinician should first assess whether the anxiety is a symptom of some other psychiatric condition, such as a major depression. Patients with obsessive-compulsive disorder may be made anxious by obsessions about danger or "germs," or if their rituals are interrupted.

Panic disorder, although uncommon in HD, is a highly treatable condition. It is characterised by the acute onset of overwhelming anxiety and dread, accompanied by physiological symptoms of rapid heartbeat, sweating, hyperventilation, lightheadedness, or paraesthesias. Panic attacks usually last only fifteen or twenty minutes, may begin during sleep, and may result in syncope. Suspected panic attacks require a good medical work-up, because most of the other possible explanations for the symptoms represent highly dangerous conditions. Once these other causes have been ruled out, the usual treatment consists of SSRIs, sometimes temporarily supplemented with benzodiazepines. SSRIs are usually mildly stimulating and may need to start at a lower dose than that used for depression.

Benzodiazepines should be used judiciously in anxious persons with HD because of the vulnerability of these patients to delirium and falls and because of their potential for abuse, especially in patients whose judgement may already be impaired. PRN medications may have to be controlled by a family member. Some patients will respond to the non-benzodiazepine anxiolytic buspirone, which can be started at 5mg two to three

times per day and advanced to 20-30mg per day in divided doses.

Sexual disorders

Many patients with HD become uninterested in sexual activity. Others may continue to enjoy healthy sexual activity well into the course of the illness. Occasional patients may desire and pursue excessive sexual activity or engage in inappropriate sexual behaviors, such as public masturbation, or voyeurism. The spouse, usually the wife, may be distressed and fearful because the individual with HD may become aggressive if sexual demands are not met. Spouses may be afraid to talk about the problem unless interviewed alone.

Interventions are difficult in these circumstances, probably because of the patient's impaired judgement and the strength of the drive. Open communication about sex between the doctor and the family can help to destigmatise this sensitive topic. With open discussion among the parties, distressing sexual behaviours can sometimes be adapted into more acceptable acts. Patients engaging in these behaviours should be assessed and treated for comorbid conditions, such as mania. We have found antiandrogenic therapy helpful in a few of these cases.

6. OTHER ISSUES

DRIVING

All patients with HD eventually lose the ability to drive. This can be a severe blow for some patients, who see driving as a sign of competence and a way of maintaining independence. In many cases, patients, with the help of their families, will realise the time has come and will voluntarily stop driving, often before their physician has come to this conclusion. Other times, however, the issue of driving can become a source of contention between patients, families, and physicians.

The Road Safety Authority advises that anyone with a medical condition which impacts their ability to drive should contact the relevant Motor Tax Office and advise them of their condition. Where a person is suffering from a progressive complaint, fitness to drive may be certified on condition that the person with a disability is regularly examined to check that the person is still capable of driving the vehicle concerned efficiently and safely.

Motor Insurance may not be valid if the person does not disclose relevant medical information. People with HD and concerned family members should discuss this with their physicians. This only applies when signs and symptoms become apparent and not to asymptomatic persons who have had a positive predictive test.

Doctors and other health professionals are considered to have a responsibility to inform patients that they have a medical condition which may affect their ability to drive. As short term memory loss is a feature of HD it may be prudent to remind a relative or carer of the patient as well.

Family members should contact the Road Safety Authority or Motor Tax Office if they feel the person with HD is driving dangerously.

SMOKING

Smoking sometimes becomes a problem for people with HD, for two reasons. Changes in the person's behavior related to disinhibition, personality changes, and perhaps boredom may turn smoking into a consuming passion, leading to irritability and even violence if thwarted. Simultaneously chorea, impairment of voluntary movements, impaired judgement, and diminished capacity for self observation may make the act of smoking unsafe. A variety of approaches have been helpful in decreasing the behavior and improving safety. Non-pharmacologic interventions include the establishment of smoking schedules and general safety measures such as ensuring that the patient does not smoke in bed, limiting smoking to rooms without rugs, and use of adaptive devices, such as a flexible tube smoker or a "smoker's robot," available through HDAI.

We have also used nicotine patches with some success. The goal is not necessarily to wean the patient completely off cigarettes or patches, but to decrease the drive for cigarettes, and the periods of nicotine withdrawal, which may worsen irritability. A variety of the antidepressant bupropion has also recently been marketed for use in smoking cessation and may be worth a try.

SLEEP DISORDERS

Sleep disturbance is a common problem in Huntington's disease, and can be due to a variety of causes. A complaint of sleeplessness may be due to a mood disorder, either

depression, or, less commonly, mania. In these cases, treatment of the mood disorder should lead to a normalisation of sleep. The clinician should conduct a careful interview and speak to the patient's family to rule out this possibility.

Good sleep hygiene is also important. Patients who do not have enough to do, and whose days are insufficiently structured may develop a reversal of the sleep-wake cycle in which they nap most of the day, and are then awake at night. This pattern tends to reinforce itself and can be hard to interrupt. Helpful strategies include sleeping consistently in a room which is not used for wake-time activities, having a regular bedtime and waking time, and enrolling in a day program, which keeps the patient occupied and prevents daytime napping. In the later stages of illness, patients may have an increased need for rest and daytime napping may be entirely appropriate, as long as the patient is sleeping at night.

Some patients will require pharmacologic treatment of their insomnia. We would caution against long-term use of benzodiazepine or barbiturate hypnotics because of the potential for tolerance, dependence, and delirium and usually prefer to use a small dose of a sedating antidepressant such as trazodone (Molipaxin), beginning at 25-50mg and increasing to about 200mg as necessary. Sedating tricyclics such as doxepin (Sinequan) or Amitriptyline can also be employed, but are highly dangerous in overdose.

It is not entirely true that chorea ceases when patients are asleep. Sleep studies conducted in patients with refractory insomnia have suggested that some HD patients have restless sleep because of a large amount of involuntary movements at night. The patient himself will often be unaware of these nighttime movements, but they will often be reported by the spouse or caregiver. A small dose of fluphenazine, haloperidol (0.5-2mg) or clonazepam (0.5-1mg) at bedtime, may suppress the movements sufficiently to allow more restful sleep. Polysomnography or referral to a sleep disorder center may be helpful in these difficult cases.

Painful leg cramping caused by dystonia and spasticity can also disrupt sleep. Treatment with a muscle relaxant, such as baclofen may relieve the problem or quinine sulphate 200-300mg.

INCONTINENCE

Most patients with advanced HD are incontinent, although this may be minimised with regular toileting. Although urinary urgency, leading to intermittent incontinence may occur earlier in the course of the disease, this is not a typical finding, and should be evaluated further before attributing it to HD alone. Causes may include neurogenic bladder, urinary tract infections, urinary retention due to anticholinergic drugs or tricyclic antidepressants leading to overflow incontinence, sedation or immobility caused by neuroleptics or sedatives, depression, dementia, or mechanical problems. Urologic consultation may be helpful in defining the nature of the bladder dysfunction and obtaining specific recommendations.

DISABILITY

The progressive nature of Huntington's disease will eventually force patients to retire from employment. Unfortunately, many patients' job performance will already have begun to deteriorate before they have received a diagnosis, or before they have made the connection between HD and the problems they are having at work. The actual difficulty is most often a problem of organisation, flexibility, and the speed of mental information processing, but the patient may appear careless or lazy, may be irritable at work, or may even be suspected of being intoxicated. This may lead to an individual being disciplined, passed over for raises or promotions, or even fired for cause when in fact the problem is a medical disability due to HD.

Therefore, early identification of HD-related problems at work is very important, for the purposes of securing accommodations at work, and eventually disability. There may also be issues of work safety. A physician or social worker may be able to help the individual inform superiors at work of the nature of the problem, decide when to take retirement, and navigate the disability application process. In our experience, many employers are sympathetic once informed, and have provided less stressful work environments and assistance with disability retirement. The Employment Equality Act may protect individuals with HD who need accommodations, but are still able to work.

Huntington's disease is a complex condition and the patient may be unable to work, but may not have a single sign or symptom which, by itself, would qualify her for

disability. Therefore, disability letters must be comprehensive, must stress functionality, and should include specific examples of dysfunction at work. Because of the particular nature of the dementia found in Huntington's disease, routine IQ test scores may not be relevant to the level of impairment because they do not reflect the organisational and task-switching problems found in Huntington's disease. Tests specifically directed toward executive function will better identify HD-related cognitive deficits.

END OF LIFE ISSUES

It is important to discuss issues related to the end of life before someone with HD loses the ability to communicate. By discussing the expected changes in advance patients can plan for the support that they and their families will need, and can have a discussion with their family and physicians about which medical treatments and interventions they think they would like to undergo, and which they would prefer to have withheld when they reach the late stages of the disease. By the late stages of HD affected individuals will have little control over voluntary movements and may not be able to walk, talk, or eat. Chorea may be suppressed, or may be severe. Death, when it comes, is usually due to the consequences of the immobility, general debilitation, and malnutrition. Pneumonia, and heart failure are typical immediate causes of death.

Huntington's disease patients and their families have a number of important decisions to make about this phase of the illness. The first concerns where the patient will be cared for. Some people wish to spend their last months at home, and receive terminal care in this setting, but others require the services of a nursing home for the final phase of their illness. This may make the patient more comfortable and relieve stress on the family. Patients and their families must decide which treatments they want if they become acutely ill, such as antibiotics for pneumonia, or CPR for a cardiac arrest. Patients who are unable to swallow will die if not given food and fluids by other means, but with a gastrostomy tube they may live for years. Improved caloric intake can increase resistance to infections, improve physical appearance, and is sometimes associated with a decrease in chorea. Others may not desire such an intervention, depending on their view of the quality of life at that time and their individual spiritual beliefs.

There are different legal mechanisms in every state by which patients can make their wishes known in advance, but it must be stressed that there is no substitute for good communication directly between patients, their families, and their doctors. The process should start early, so that difficult topics can be introduced gradually, in an unhurried manner, and so that the conversation can take place while the patient retains the ability to communicate.

It is also important to readdress these issues periodically. An advance directive reflects a person's ideas at one discreet interval, often several years in the past. For example a blanket statement such as "I would never want a feeding tube," made shortly after the diagnosis of HD, may be revised as the patient and family gradually adapt to increasing disability.

Table 18: End of life issues

- In-home versus outside care
- Gastrostomy tube feeding
- Life sustaining emergency measures (e.g. CPR, intubation)
- Use of antibiotics to treat infections
- Other specific care issues (e.g. treatment of other ongoing health problems)
- Guardianship, Advanced Directives and "living wills"
- Autopsy / brain donation for research

One must avoid overgeneralisations about "end-stage HD." An intervention that is right for one person may not be right for another. For example, many patients who can no longer eat safely are still able to talk and are fully aware of their surroundings. In one instance a man was told that placement of a gastrostomy tube would reduce the number of aspiration pneumonias from which he suffered. He replied that eating was one of his few pleasures and he preferred to take this risk, knowing that it might shorten his life.

In another instance, a teenaged girl with juvenile onset HD had become very rigid and was unable to eat. A ward of the state, she was initially denied a gastrostomy tube by her official guardian who believed that such interventions were "futile" and "only prolong suffering." This decision was reversed when her foster mother strenuously pointed out that the girl was in no pain, was enjoying activities and family life, could still talk, and in fact had been asking for the tube all along.

For other individuals, the issue of a gastrostomy tube does not arise until the patient no longer seems aware of his surroundings. In this circumstance, it often seems best to a family not to prolong the process artificially, but to support the patient's comfort and let him die a natural death.

Some people with HD may wish to donate their brain tissue for research. Information is available from the HDAI office. We hope that, where possible, patients and families will discuss this decision with each other in advance and will also inform the staff of nursing homes and hospices of their intentions ahead of time. The cost of autopsy and transportation to and from the funeral home are usually born by the institution receiving the donation, and the brain can be removed quickly so as not to delay burial and in such a way that it does not show and will not interfere with viewing. These generous gifts, made at a sad time, may give the person's death great meaning. Each one moves us closer to the day when no one will have to die from Huntington's disease.

APPENDIX 1:

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APPENDIX 2:

PREDICTIVE TESTING FOR HUNTINGTON'S DISEASE

National Centre for Medical Genetics

Our Lady's Children's Hospital
Crumlin, Dublin 12. Tel: 01 409 6902
www.genetics.ie

APPENDIX 3:

HUNTINGTON'S DISEASE ASSOCIATION

Huntington's Disease Association of Ireland (HDAI) is a national voluntary organisation established by Huntington's Disease (HD) family members to provide consultation, information and individualised support to those diagnosed with HD, their families and their health care teams. The Association was formally launched in 1985 and was incorporated in 1988. HDAI is a registered charity CHY 10130. HDAI exists to provide a unique service offering comfort, information and support to all those affected by HD.

HDAI offers:

- A national information and support service based in Dublin which provides information and support to families; individuals at risk of HD; carers and health professionals; HDAI liaise with service providers; highlights the needs of members and creates awareness of HD. Confidentiality is respected.
- A Family Support Officer is available to meet family members in crisis.
- Access to counselling for those in need.
- Support group meetings/carers workshops in Dublin, Cork, Mayo/Roscommon and Limerick.
- An annual information meeting and respite weekend available to people with HD and their families.
- Publications including leaflets, booklets and articles covering the many issues specific to HD available for families, social care and health professionals on request.
- Information through a quarterly newsletter and annual magazine.
- The loan of a specialised HD Chair which helps protect against injury related to involuntary movements and debilitation.
- Talks and information seminars on request.
- Therapeutic treatments for patients in the mid-stages of HD.
- HD ID cards provided on request (free-of-charge) to people with HD.

For further information please contact:

Huntington's Disease Association of Ireland (HDAI)

Carmichael Centre, North Brunswick Street, Dublin 7.

Tel: (01) 872 1303. Freephone: 1800 393939.

Email: hdai@indigo.ie

www.huntingtons.ie

Symbol of the International Fight against Huntington's Disease

The main theme of this symbol of the International Huntington's Association is a logo depicting a head and shoulders, representing the threat of Huntington's Disease to both mental and physical capabilities. The reduced size of the inner image indicates their diminution in the sufferer.

This symbolic design, also reflected in our cover design, appears as the flower of a growing, vibrant plant, and is protected within its leaves. The purpose, growth and development of the International Huntington Association is thereby illustrated, together with the increasing worldwide concern that this disease shall be tamed.



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